some surgeons will report just the cataracts that are creating visual problems for the patient, and some opacities that are not decreasing the visual acuity would not be reported.

Also, there is such a variation in the age of the patients included, and also such a variation in the follow-up considered, and in some studies they would say that the follow-up is from three months to two years, but in fact maybe just two patients had the follow-up of two years and the great majority were followed up for six months only. And in some studies -- for example, for the ICL -- during the same study different models of the same design were implanted, and you know with different vaulting characteristics, so the effect for cataract formation would not be the same.

So there is a great need of standardization of these studies evaluating cataract formation. First of all, the parameters used for the YAG iridotomies should be described, because eventually this is cataractogenic. All trauma to the anterior capsule during this surgery should be noted for future reference. A follow-up period should be at least two years because in fact, according to the literature, the majority of cataracts appear between one and two years after the procedure. And of course, we have to evaluate very nicely the relationship of the phakic lens

with anatomic structures because the contact is one of the most important factors.

Also, of course, we need a very accurate method to choose the IOL size. To use just the white to white to choose the overall size of the lens that's going to be implanted is not accurate at all, and that's why we're having so many complications, and this could really be avoided.

There is a need of evaluation of subclinical inflammation with laser flare meters because in some cases, there was a very good vaulting lens and a cataract appeared anyway.

There is a need of evaluation of explanted phakic lenses with histopathological analysis of adjacent tissues, but if you ask me right now if just with histopathologic studies alone we will be able to differentiate cataracts caused by the surgeon and cataracts caused by the lenses, the answer is that we don't know yet. We have just one specimen and we would like to look for more specimens to have an impression about that.

And of course, we need to describe the evolution of the anterior subcapsular opacity.

So let's talk about the possibility of a classification for cataract formation after phakic IOL implantation. So as I mentioned, some surgeons would say

that all the opacities they saw are peripheral and they are non-progressive, but we have this paper indicating that the peripheral superior opacity progressed, involving the optical zone. So if you have a classification, we should maybe classify the opacity in each visit to have an impression about the progression of the problem.

So as you know, there are systems for the classification of cataracts and they are all based on standard retroillumination photographs and the total area of the opacity. These are three well-known systems, the LOCS system, Wilmer system, and Oxford system.

Here, we have some pictures showing how to classify nuclear, cortical, and posterior subcapsular cataracts with the LOCS system, all based on these standard photographs. This could eventually be applied to cataract formation after phakic IOL implantation. This is how we grade the cortical opacities according to the Wilmer system and this is the way we score anterior subcapsular and posterior subcapsular opacities according to the Oxford system.

Also, there are very sophisticated systems combining high-resolution digital retroillumination imaging with image analysis systems, allowing objective and quantitative measurement, for example, of posterior capsular opacification, which eventually would be very

useful in this clinical situation.

So in a way, if there is a way to do a classification, this classification should indicate the location of the opacity. For example, peripheral or paracentral or central opacity. Also, maybe there is a possibility to have an index for the intensity of the opacity, and of course, we would have to score the area of the opacity, and by doing that in each visit, we will have an impression about the evolution and the progression of the opacity and we would really understand better the phenomenon.

Thank you very much for your attention. Thank you very much again for the opportunity.

DR. WEISS: Thank you very much for an excellent presentation. Would you be able to take a seat at the table, and we'll open up to the panel for some directed questions.

Dr. Bandeen-Roche, then Dr. Matoba, and then we'll continue around. Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Yes, I want to thank you for your presentation -- very clear -- and your careful recommendations about the data to collect involving the surgery I think was great.

Just one brief question. You talked about the importance of tracking the evolution of the cataract and

discussed grading. What implications do you think there are for the frequency of evaluation and do you think that that should be by passive surveillance or by active surveillance? Just elaborate a little bit more on how to track the evolution of cataract.

DR. WERNER: I don't have a precise idea about when all these gradings should be done. Of course, immediately after the postoperative period, within one month to anything that's very fast developed, and maybe six months, one year, two years, because this is what we see in the literature.

But this is not only to just have the score. It's also for us to understand the phenomenon because still there are many surgeons who believe that the cataract is really not a problem because they have just opacities in the periphery that never progress, and we need to understand if they are not really progressing or he is just not observing.

DR. BANDEEN-ROCHE: Thank you.

DR. WEISS: Dr. Matoba?

DR. MATOBA: In regard to the development of cataracts in areas of contact between the IOL and the crystalline lens, how much do you think the lens material or the nature of the lens material contributes or is it mostly, you think, a mechanical effect?

DR. WERNER: Well, I don't know if I can answer this question because we only have results about the ICL, which we know the material. There is another lens made of silicone and I'm not aware of their results, so we cannot really compare if there is a material effect.

Also, as I mentioned, there are papers showing that cataract is formed only in the area of contact. Other papers would say that it was formed in a different area, but maybe the follow-up was not enough. So there are still many questions about that.

DR. WEISS: Dr. Bradley, Dr. Huang, and then Dr. Mathers.

DR. BRADLEY: Just a clarification on the peripheral cataracts you described. How peripheral are they and, for example, would they become visually significant under nighttime viewing conditions where the pupil would dilate?

DR. WERNER: Well, when you look at the literature, it is really not described, and sometimes, in very early papers, they would describe some peripheral opacities that would cause some glare in light conditions of evening or something like that. But talking to surgeons, they would say that the peripheral opacities which are barely visible in the pupil dilation, they would not cause any problem.

DR. WEISS: Dr. Huang?

DR. HUANG: Two questions. The first question was regarding your earlier presentation, you seem to have implied there were two types of cells that were induced in the two different locations of the cataract. One is A-cells induced in the anterior capsule, and then E-cells induced in the posterior capsule. Is there any vital stain that can help you to distinguish what type of cells are responsible for the evolution of this cataract?

DR. WERNER: When you perform histopathological studies, in fact what you see is that both cells are always involved in everything, but there is always a predominate type. For example, even for PESU, you have a fibrotic form of PESU and you have a firm form of PESU, and when you perform normal stains, you can see even morphologically they are very different because E-cells always have the tendency to be bloated, and the other are elongated fibrotic cells, fibrotic-like cells.

DR. HUANG: In the LOCS III grading system, it's really a numerical system and there is a highly individual variation. Do you have any suggestion how to standardize if that system were to be chosen for the cataract characterization? And also, I believe the LOCS III does not have any geographical information about a cataract, and so do you have any suggestion how to modify

the system?

DR. WERNER: I believe there should be a geographic thing because it's very important for the areas of contact who are outside the contact of the lens. So in this case, it's very important.

But with regards to your first question, I think we should start by collecting many pictures from surgeons to create standard pictures, as they have in the LOCS system, and we have some, but we need more pictures to have really different grading if we use such a system based on standard photographs.

DR. WEISS: Dr. Mathers?

DR. MATHERS: Do you think that the photographs, the retroillumination of the opacification, can the photographs detect smaller anterior subcapsular cataract formation than the slit lamp can detect it? What do you think is actually the finest, highest resolving method?

DR. WERNER: We have experience with these systems based on retroillumination photographs for posterior capsular opacification, and this is the best we can have for that.

DR. MATHERS: Do you think that's higher resolution than the human eye achieves with the slit lamp?

DR. WERNER: Eventually, yes.

DR. MATHERS: Yes. And have you any experience using confocal microscopy, which could actually focus onto the anterior capsule and have even higher resolution? Do you think that that's possible?

DR. WERNER: Well, my own experience with confocal microscopy regards the cornea, and I know that there are some objectives which you could switch in some devices and have an imaging of the anterior surface of the crystalline lens. I have no experience with that and I don't know if there is any data available published about that.

DR. MATHERS: Sizing is clearly an important process here. Do you think that the high-resolution ultrasound will give the best sizing data and can that be used clinically to determine which size to put in?

DR. WERNER: We are evaluating this right now with these cadaver eyes. The results have been very interesting. So I don't know exactly the status of development of the technique, when it's going to be available -- maybe this year -- but apparently it's the best we can get for the moment.

DR. MATHERS: Do you think that the issue of visual significance could be assessed best with glare testing or what would you suggest as the most significant, highest-resolving method to test the small amounts of

visual impairment you might get from an early cataract?

DR. WERNER: Yes, it is a very good question, because in some cases discussed with the surgeon, the lenses were explanted because of glare, and not really decreasing visual acuity. So glare is very important.

DR. MATHERS: You think it's better than contrast sensitivity testing as it's normally performed?

DR. WERNER: Maybe both.

DR. MATHERS: Just your opinion.

DR. WERNER: Maybe both should be associated in this case, yes.

DR. WEISS: Mr. McCarley, did you have a question as well?

MR. McCARLEY: One question just quickly. In your experience, and maybe one of the clinical ophthalmologists can answer this maybe even better, a cell flare meter is used to determine subclinical inflammation. Is that different in a posterior chamber lens than it would be, for instance, in an anterior chamber lens?

DR. WERNER: Well, what we saw in the literature is that there are also increased values of flare cell meter with anterior chamber lenses, and apparently the values are even higher and they also stabilize above the preoperative values, contrary to cataract surgery, where you have higher values, but these have a tendency to come

back to preoperative values after one year or so.

DR. WEISS: If there are no other questions, I want to thank you, Dr. Werner, for your excellent presentation.

We can move on to the open public hearing session. Is there anyone who wanted to make any statements?

(No response.)

DR. WEISS: If not, I'm going to put a question to the panel. If we have perhaps a 15-minute coffee break and skip lunch, we might be able to catch earlier flights, as I know is in the interest of some. Are any of you interested in doing that, taking a 15-minute break, rather than -- so we have two hands up for Dr. Bullimore and Dr. Matoba, and Dr. Mathers for sure. I would say that passes without a formal vote.

So we'll take a 15-minute coffee break and we'll see you back here in 15 minutes.

(Recess.)

DR. WEISS: We will now start the FDA presentation and Donna Lochner will introduce the questions for panel discussion.

MS. LOCHNER: Yes. I'm just going to go through the questions and give a little bit of background to where we were coming from with each question.

We're going to begin today with the endothelial cell density study. After I've stepped through this question, I'll turn the floor over to Dr. Grimmett, and then the panel will discuss the endothelial cell issue before going on to the next questions.

First, "Please comment upon the inclusion criteria recommendations found in Table 1." This topic is still being actively discussed, and particularly with the ANSI Standards Committee, and so we believe any comments will be very timely.

Table 1, which is just shown right here, provides the recommended minimum endothelial cell densities, and these values for minimum endothelial cell density are generally being used in current U.S. phakic IOL studies. These values were determined over the course of several meetings over the years with input from FDA, industry, and ophthalmologists that attend these standards meetings. Allow me to hopefully clarify how the minimum densities per age category were determined.

This slide is included as Attachment B in the handout. First, the approximate initial cell density for a 21-year-old, as shown in the second column in this table, was taken from the 1997 Moller-Pedersen article and the citation for this article is provided in the handout, but not on this slide.

For the 35- and 46-age categories, the cell density at time of implant was approximated by assuming .6 percent yearly cell loss due to normal aging, with the .6 percent figure taken from the 1997 Bourne article, as referenced earlier by Drs. Edelhauser and McCarey. This was done to provide a check of whether the minimum inclusion criteria per age group were reasonable.

The third column, the estimated rate of cell loss per year, represents potential rates of loss due to the phakic IOL. In other words, 1.5 and 2 percent assumed loss from the phakic IOLs were used as examples to then calculate the age when the cell density would be less than 1,200 cells per millimeter squared and less than 1,000. These ages, shown in the fourth and fifth columns, assume a surgical loss of 10 percent and compound the 1.5 and 2 percent loss annually.

Finally, in order to determine the minimum cell density inclusion criteria, we looked at the starting densities that would ensure greater than 1,000 cells at age 70 for the 21- to 25-age range, and at 75 for 26 and older.

So this table verifies that the minimum inclusion criteria, as shown on Table 1, would be sufficient in a worst case situation to allow for adequate cell density for the health of the cornea for roughly the life of the patient, assuming a 2 percent annual loss from

the phakic IOL and that patients would have at least 1,000 per millimeter squared at ages 70 to 75.

As you can see, there are various assumptions inherent in the inclusion criteria and because of the iterations this has undergone because of the committee process, we are very much interested today in the panel's comments on this inclusion criteria.

Our statistical calculations suggest that 200 subjects should be sufficient to detect a 2 percent loss using measurements at multiple visits in order to establish linearity of the loss. The measurements, as currently proposed, would taken at the three- or six-month visit, the 12-, 24, and 36-month visits.

Further, although the statistics suggest that 200 subjects would be sufficient, we recommend that specular microscopy be performed on all subjects enrolled in the study to ensure that 200 analyzable photographs are obtained.

Last, we recommend that multiple images be captured at each visit and the mean endothelial density from those multiple images be used in the analysis.

We are asking for panel comments on these criteria as well.

Now, I'd like to turn the floor over to Dr. Grimmett for his review.

DR. GRIMMETT: Thank you, Donna.

This is Michael Grimmett. I've prepared some comments in outline form which at least the panel members should have on their table. It's a 10-page outline, and I promise to go very quickly through it. There are four tables as well.

Regarding the questions, I think I'll go through my outline first. I was doing the bulk of this thought process and review prior to having the questions. I was doing the work, I'd gone on vacation out in Santa Fe, and I'm relieved and grateful that in the open public hearing session, my wife did not comment on the timing of that review.

(Laughter.)

DR. GRIMMETT: Notwithstanding that, I think I'll do this review first, and then we'll come back to the questions if some of the issues are not resolved.

Just in general, and some of this has been alluded to by the previous speakers, the peer-reviewed literature on phakic IOLs has numerous limitations, and it's important to recognize that when reviewing any data that's reported in the literature. Mostly, the data are retrospective in design, they're non-randomized case series, they have extremely low numbers of eyes reported, there is poor accountability for the longer follow-up

intervals, and in general morphometric endothelial analyses are not generally reported. So coefficient of variation and percent hexagonality are not there.

Additionally, my review is not exhaustive or comprehensive.

I think it's instructive to look at phakic IOL types because we can separate them into three different animals that have different implications for the corneal endothelium. I've separated them into anterior chamber type and posterior chamber type. Of the anterior chamber type, there are two, angle-supported and iris-fixated.

Looking at the literature on the angle-supported lens, I'll just give you a smattering of some articles to go over what are reported endothelial cell losses and what's known about design parameters that would impact our recommendations regarding future phakic IOL studies.

To start with, angle-supported lenses, a first-generation lens, the Baikoff ZB lens, had a distance between the IOL edge and the endothelium of only 1.16 millimeters, and that was the key factor. It was determined that there was a high endothelial cell loss secondary to excessive contact between the IOL optic edge and the endothelium. One report by Jimenez-Alfaro reported a 16 to 18.8 percent loss at one year and a 20 to 28

percent loss at two years. Another report reported up to 56 percent loss with a shorter follow-up. Of the second report, 37.5 percent had morphologic or cell density changes.

Quotes in these articles include "We have stopped doing this surgical procedure" and "Further implantation of this IOL is unacceptable."

The second-generation lens, the Baikoff ZB5M lens, was manufactured until 1997. The major difference here is that they increased the distance between the IOL edge and the endothelium, increasing that to 1.56 millimeters. Endothelial cell loss in one study was reported at 4.5 to 5 percent cell loss at one year, 5.6 to 6.8 at two years, and 5.5 to 7.5 loss at three years.

A separate study by Perez -- forgive me for my pronunciation -- Perez-Santonja found an endothelial cell loss of 12.33 percent at one year and remaining relatively stable at two years.

Then the larger study was recently reported in Ophthalmology found that at one year there was a 5.53 percent loss, and interestingly, after year 2, while the numbers fell down significantly in terms of total eyes examined, the overall loss approximated normal aging losses. That is, preop to year one was at 5.5 percent loss; year 1 to year 2, 1.37 percent loss; year 2 to 3, .72

percent loss; year 3 to 4, there was a .28 percent loss; year 4 to 5, there was a .55 percent loss; year 5 to 6, .37 percent; and year 6 to 7, .56 percent.

So based on this study, and the reason I find this instructive, is that they give us some information regarding what is a reasonable duration to follow these particular lenses before they come to the panel. If we take this data, which is one of the largest subsets that I could find in the published literature, in year 3 they still had 157 eyes, albeit they're mixing lens times. They're either started or stabilized, and they found stabilization from the two- to three-year period, and you can tell three years is the appropriate duration of a study.

A fourth-generation lens, ZSAL-4 by Morcher, had a distance from the IOL edge to the peripheral cornea of 1.65 millimeters and they reported an endothelial cell loss of 3.5 percent at one year and 4.2 percent at two years, albeit the numbers are low. There are only 18 eyes. They commented that there is a fifth-generation lens, but I could not locate it in the published data regarding this product.

Another anterior chamber angle-supported lens in the literature is the Nuvita lens by Bausch & Lomb, and it's a single-piece PMMA IOL. In one study of 21 eyes by

Allemann in Ophthalmology, they reported a 10 percent cell loss in the first year, another 4.3 percent in the second year, and, given these large numbers, certainly if that were to come to the panel, I would want to see more data.

The next category of anterior chamber lenses are iris-fixation lenses. A Worst-Fechner lens developed in the late '80s, one particular study just reported two eyes of greater than 50 percent cell loss, but they didn't provide any mean cell density analyses or morphometric analyses. A separate study in 1996 by Perez-Santonja reported a 13 percent loss at one year, another 4.6 percent at two years, indicating to me that the central endothelial cell loss did not stabilize over a two-year period. The N was only 30 in this particular study.

The Artisan or Iris-Claw lens, the prior nomenclature which is unfortunately called the Worst Iris-Claw lens --

(Laughter.)

DR. GRIMMETT: Those are synonymous as far as I understand. There may be some design changes I'm not aware of, but I believe they're in the same family.

It had reported some distances from the corneal endothelium in various publications. For example, a -15 diopter lens with a 3.2 millimeter anterior chamber leaves 1.97 millimeters from the corneal endothelium. Because

these lens are fixated at the iris itself and not vaulted above the iris, certainly you would expect more distance, and this is what we're seeing. There's more distance from the endothelium. So the angle-supported lenses, in my view, given their proximity to the cornea, have a higher risk to the corneal endothelium than, let's say, an Iris-Claw lens, assuming that the anterior chamber (inaudible) is constant, whatever it happens to be.

Looking at some data regarding endothelial cell loss on the Artisan lens, a study by Menezo showed a 6.6 percent loss at 12 months for 109 eyes and 9.22 percent at two years, but I think it's instructive just to look at the differences. It's 6.6 percent preop to year 1; 2.63 year 1 to 2; 2.5 percent year 2 to 3; 1.74 year 3 to 4.

They found that the cell loss correlated to increased power of the lens, the thicker lens -- that is, perhaps closer to the endothelium -- and shallower anterior chamber depth, which would also tend to bring the lens closer to the corneal endothelium.

This particular study reported morphometric measurements regarding percent hexagonality and coefficient of variation.

They also find some changes that I found instructive. They found that there were statistically significant decreases or changes at six months and then

return at approximately two years with gradual resolution back to near preop factors in their four-year study.

Then the final category of lenses would be posterior chamber lenses, which we've heard a great deal about already here today by the speakers. Dr. Werner's excellent presentation showed us pictures of the Fyodorov posterior chamber lens, which is not in general clinical use, with cell losses of 10 percent at 12 months.

Interestingly, the Chiron Adatomed lens that Dr. Werner indicated was pulled because of cataract formation, at least the two studies I pulled, did not report any endothelial cell data whatsoever, reports by Fechner and Marinho. I didn't locate any other studies on those lenses.

The Staar Surgical ICL that we heard about today already, one study by Zaldivar of 124 eyes didn't report endothelial cell counts, and in another study by Arne, cell loss was actually remarkably low, 2 percent at 12 months and 2 percent at 24 months, and no eye had an endothelial cell loss greater than 3.8 percent at one year in 58 eyes. Since these lenses are in Phase III trials, I'm certain there's some data targeted and reviewed by the FDA in a confidential fashion regarding larger sample sizes.

Knowing what the literature has to say about

endothelial cell loss and the differences between these three types of lenses would help us give guidance regarding future manufacturers' studies. It's important, as Dr. Edelhauser alluded to, to look at normative data, so that we know what the natural rate of loss is for corneal endothelium in order to gauge our comments.

Rates of normal endothelial cell loss range between .3 and 1 percent per year, depending on where you look. I've quoted the various studies. The Bourne article in 1997 with the .6 percent rate is frequently quoted, but there are slight differences in the literature in that regard. It's in somewhere in that range.

As far as surgical procedures, we all know that operative procedures can create both a direct surgical instantaneous hit to the endothelium as well as possibly change the annualized cell loss rate. Cataract surgery as far as Bourne's article in 1994 reported a mean 2.5 percent cell loss per year over a 10-year period. It's important to realize that these were intracapsular and extracapsular surgeries with iris-sutured lenses, transiridectomy clip lenses, and a few posterior chamber lenses. There are some other articles that indicate that cataract surgery causes a 1.1 percent cell loss rate per year, and a Werblin article in '93 said that one year is an 8.8 percent loss, and you'll note that in the FDA table previously shown by Ms.

Lochner and in some of the assumptions I'll later make, we just round that figure to a 10 percent surgical loss at the time of the procedure, which obviously is different from the future cell loss rate that may be increased over normal.

As a point of interest, penetrating keratoplasty has a 7.8 cell loss per year.

I went ahead and quoted the age-stratified normal endothelial cell density values, both from the Yee article in 1985 as well as a pathologic analysis. The difference between the studies, one is specular microscopy, the other is pathologic. I found they were similar in terms of mean values. The lower age bracket, age 20 to 29, they start at 2,900 cells and by the time you get up to age 80-89, there are 2,300 mean cells. The main difference is in the standard deviations.

Dr. Edelhauser earlier indicated that the non-contact robo data agrees with the Yee data, and I quite frankly find the standard deviation values in the path study to be huge, plus or minus 500, plus or minus 690. In talking with Dr. Edelhauser on the break, he's going to look further into the Moller-Pedersen article regarding the standard deviations, but I tend to gravitate toward the Yee article with the standard deviations.

The peripheral cornea, if measured, is known to

have increased cell density. Per some data that Dr. Edelhauser provided, there's a 5.8 percent increase in cell density in the paracentral region and a 9.8 percent increase in the peripheral cornea.

The next category that I did, knowing the peer-reviewed literature and now knowing normative data, is I tried to determine what would be some thresholds for unacceptable rates of endothelial cell loss. There are two different questions, I believe.

One, as a panel member, when an application comes to panel, we all be concerned about what is an acceptable cell rate when we get that application with a particular observed cell loss rate. The reason it's important to get some judgement about acceptable cell loss rates now is it will help us give guidance regarding what or how low should thresholds be that we're actually trying to screen for to make the determination how big the sample sizes must be. So we have to have a sense for what are the maximum and minimum ranges for thresholds that we're even looking at, so we can give some type of guidance regarding sample sizes.

I certainly don't expect anyone right now to define an acceptable cell loss rate. That will certainly be a hotly debated topic once an application's received, but I think it's instructive that we go through the

exercise to see what our limits are, maximum and minimum unacceptable rates of cell loss.

I've approached this argument by first looking at life expectancy data. The RP-2000 mortality table is based on a study of the mortality experience of pension plans conducted by the Society of Actuaries and was in response to pension legislation that directed the Secretary of Treasury to promulgate the use of updated mortality tables for various pension calculation purposes.

According to that table, the life expectancy for a 21-year-old male is 58 future years or an age of death of 79. The life expectancy for a 21-year-old female is 62 future years, so an age of death of 83. Those are United States data.

Realize that depending on your entry date, you'll have change, obviously, to your age of death. If you enter at age of 80, you don't have an age of death of 79.

(Laughter.)

DR. GRIMMETT: But I used it as a fixed value for this particular analysis, so as to not get confused with multiple iterations of the tables. Suffice it to say that when you enter at 20, 30, or 40, it may only differ by a few years in terms of your age of death.

The minimal acceptable corneal endothelial cell

density value is critical, and Ms. Lochner presented a table regarding a 1,200 threshold and a 1,000 threshold near death. I picked values on either side of the range to show the range of acceptable cell loss for sake of argument.

In one of Dr. McCarey's earlier versions of a slide, he quoted a minimal acceptable rate of 1,500 cells. Whether we call that number 1,500 or 1,400 or 1,300 or whatever it's picked as is not really the crucial value, but I think a larger number has the argument that if these patients get into any kind of trouble with their phakic IOL, number one, it allows you to do a surgical procedure to possibly correct that, whether it be explantation of the IOL or manipulation of the IOL.

Secondarily, we all know as clinicians that as patients enter their early 70s, they have a much higher likelihood of having us see them with cataracts just from age-related phenomena. Whether or not it's increased with phakic IOLs remains to be determined, but this larger target value near or at the age of death will certainly allow a future intraocular surgical procedure, such as cataract surgery. If we run all of our calculations and run them right down to the wire and leave them the bare minimum and leave half of the years to the time of death, you are not giving that patient the opportunity to have any

intraocular intervention of any kind. So that's why I picked the number of 1,500, and Dr. McCarey in an earlier version happened to put that number there, so I went with it.

The next number I used is a potential corneal edema of 800 cells per square millimeter. Acceptance of this particular target will not allow a future intraocular procedure, in my opinion, and certainly if I had a patient of advanced age with immense nuclear sclerotic cataract requiring higher phaco times, I would not be comfortable performing phacoemulsification with entry cell count of 800. I would certainly advise the patient clinically that they would have a higher chance of having postoperative corneal edema.

In the literature, there's been a quote of 500 cells for imminent corneal decompensation, but I think it depends on the actual function of the remaining cells. So the exact, precise figure is not locked down, but in my opinion, clinically it's somewhere in the area of 800.

The assumptions I made for my threshold analysis is that the endothelial cell loss, as calculated, was an instantaneous, exponential endothelial cell loss rate, that they lose 10 percent at the time of the surgical procedure, and then they have a continuous stable annualized exponential cell lose rate after that time. I

used a round down analysis of any remaining fraction. I used .99 rounded down because partial cells do not survive.

I did not alter the life expectancy target values, as I had previously mentioned.

Table 1. I'm not going to go through this, obviously, in detail, but all I did is create an Excel spreadsheet with a formula. I set the target at the end at 1,500, I set the percent drop per year, and I was back-calculating the cells you would need to enter the study. That's all it is. So I was trying to find out what cell count would you need at age 21 in order to end up with a cell count of 1,500 at the time of death for male or female, and then supplying the percent drop per year.

For that particular assumption, 1,500 cells at the time of death, 2 percent cell loss per year, I found, for example, age 21, you need 5,900 cells if you're female and you need 5,400 male. Not possible. We looked at the normative data and those numbers exceed the normative data.

So the conclusion from that scenario is that if a 1,500 cell target is desired at death, a 2 percent annual cell loss rate is not acceptable. It's not possible to enter with a high enough cell count for all but the very older age ranges. So everyone will fall below 1,500 because you can't enter with a high enough cell count.

I did that same type of analysis trying to

bracket what would be inclusive of all ages in order to allow everyone to enter the study. A 1.5 percent cell lose rate, which is Table 2, they're still entering with some very high cell counts. At age 21, for example, 4,300 for a woman and 4,100 cells for a male.

The conclusion from that scenario with 1,500 target and 1.5 percent cell loss is that no one could enter with a high enough cell density, except those older than approximately 50. So that cell loss rate is unacceptable, the 1.5, if you're targeting for 1,500, that target, of course, having the advantage of allowing someone in the future an intraocular surgical procedure.

It turns out a .9 percent cell loss rate per year allows all ages to enter with a reasonable cell count that could be achieved based on the normative data. The .9 percent cell loss per year on Table 3 shows all the entry cell requirements, and they reasonably match or were below the normative data for all ages, telling us that the cell density values will approximate or exceed 1,500 at the time of death for all patients entering the study.

So the .9, assuming you'd want 1,500 to be your target, is the maximum allowable rate that's inclusive of all ages, and that rate is approximately 50 percent higher than the normal of .6 percent cell loss rate per year. We'll later hear from our statisticians regarding the

feasibility of trying to read for that low level of cell loss rate in the face of the variability and precision issues that Dr. Edelhauser brought up, because it's my opinion, based on review of some initial data, that the sample sizes would have to be unreasonably large.

Just as an example from the literature, an angle-supported phakic IOL from Alio, 1999, has a cell loss rate of .72 percent from years 2 to 7 after experiencing a 6.83 percent loss from preop to year 2. So based at least on something in the literature that the numbers are not huge, it's doable.

Looking at it a different, looking at the target of 800, so running right up to the edge of corneal edema, I can give you all the tables, but the number that I am giving you is 1.9 percent cell loss rate per year. That number of 1.9 percent cell loss rate per year would allow all patients to enter based on the normative data.

So if you desire an 800-cell target value, a 1.9 percent rate of annual endothelial cell loss is the maximum allowable rate of loss that's inclusive of all ages, and that's about three-fold higher than the normal .6 percent rate per year, and at least based on the Menezo 1998 Artisan lens data, I have an average cell loss rate of 2.28 percent from years 1 to 4.

Based on all these analyses and review of the

literature, I went ahead and just prepared a bunch of different issues that I would want to see or issues that I would want considered in phakic IOL studies regarding the endothelium, and then we can back to the specific endothelial questions. Most of the question issues I believe will be covered.

General issues that I would have for all phakic IOL studies is that certainly endothelial cell density measurements are mandatory. We saw in some of the published literature it did not report endothelial cell densities whatsoever, which I think is unacceptable for a new product of this design because it's a critical issue for the survival of corneal health.

Certainly, a central count is mandatory. A peripheral count will be important, especially if it's an anterior chamber lens. You'd want a cell density in the region near the IOL edge or in the area of minimum distance between the IOL and endothelium. That was learned from early lens design. So especially with an angle-supported lens, I would be highly interested in reviewing the peripheral cell count.

It is my belief that morphometric analyses are mandatory. We know that analysis of cell shape and size provides a more sensitive indication of endothelial cell damage than cell density alone. I understand the

limitations of the issues, as Dr. McCarey and Dr. Edelhauser have outlined, regarding the coefficient of variation and the reliability, especially with the algorithms of the non-contact robo. Notwithstanding those limitations, I still feel it's an important variable to consider and may give us some additional information.

Just as a matter of course, corneal pachymetry, corneal functional analysis, most certainly would be suggested.

The duration of the study that I would be interested in prior to that study coming to panel would be three years. Based on the literature, it seems like there is an initial larger decrease and subsequent next decrease, and then stabilization after a year or perhaps two to three. Depending on what is seen in panel, it would be my guess that there would be discussion of postmarket surveillance of endothelial cell data for possibly a year or two more.

There are some data that it may take four years to see the morphometric data return to baseline levels and ensure stability, but I do not believe, based on what I've seen in the peer-reviewed literature and based on my concern about the corneal endothelium, especially for anterior chamber lenses, that I would be comfortable approving a lens with only two years of data. So for me,

three years would be the minimum I would favor.

I would favor a longer endothelial study duration, perhaps postmarket-mandated, for higher risk factors, such as angle-supported lenses, which have a higher risk to culture the endothelium than iris-fixated lenses, which are closer than posterior chamber lenses.

The same issue. Thicker lenses are closer to the endothelium than thinner lenses. So we would want longer follow-up for those.

A shallower anterior chamber depth, such as hyperopic patients, would have a higher risk than deeper anterior chamber depth, perhaps if the IOL is closer to the endothelium, and certainly chronic anterior chamber inflammation, as previously mentioned, would be a higher risk factor for endothelial loss than a quiet anterior chamber.

Interestingly, in one early, approximately 50-page paper by Drews in 1991, he went over study parameters versus the FDA grid regarding what he would expect for phakic IOLs, and he recommended a five-year study duration. I certainly don't disagree with that, given the importance of corneal endothelium.

With respect to anterior chamber phakic IOLs, we know that the optic-endothelium distance plays an important role in potential endothelial damage. Therefore,

high-resolution ultrasound, as mentioned by Dr. Werner, I believe would be mandatory to disclose the optic-endothelial distance and distances between other eye structures and the IOLs, such as the crystalline lens.

The peripheral endothelial cell density and morphometric measurements would be mandatory in my opinion in the region of the IOL optic edge, in addition to the central endothelial analysis, because if the examination is limited to the central cornea, it may fail to detect significant endothelial injuries, and then specular images can show significant morphologic changes over the edge of the IOL in the absence of central cell density changes.

I would caution that a preop history of eye rubbing may be a contraindication for entry into the study, especially when we're talking about such low tolerances between the distance between the IOL edge and the corneal endothelium.

Depending on the IOL design, such as an angle-supported lens, a manufacturer must specify a minimum anterior chamber depth that contraindicates IOL insertion.

Because chronic inflammation is a known factor in endothelial damage and because some studies have disclosed chronic anterior segment inflammation after phakic IOLs using a laser flare cell meter, I would recommend laser flare fluorophotometry to evaluate chronic

anterior chamber inflammation, and just raise the question would iris fluorescein angiography be of any help if a lens were either rubbing the iris or directly affixed to the iris? So that would be an issue that perhaps in a small subset of patients in early studies may be relevant.

Posterior chamber phakic IOLs certainly would have advantages for corneal endothelium. They would have a maximum distance between the IOL and the endothelium. They would avoid optic-endothelial contact, but of course, their location behind the iris would have a higher risk for pigment dispersion and introduction of cataract. If these lens induce chronic anterior segment inflammation, they certainly may have secondary effects on the endothelium, so I do believe that endothelial studies are also important for posterior chamber lenses, irrespective of the fact that they're the furthest lens away from the endothelium.

As far as that table -- now getting back to the two questions, I added these last two portions right at the end. Getting back to the table, what would be the recommended minimum endothelial cell density to enter these studies? And we saw that table put forth by the FDA.

I see two approaches to attack the problem. One is standard deviations. You could look at accepted normative data and say you don't want anyone entering the study outside of, let's say, lower than, let's say, two

standard deviations.

Let's talk about two standard deviations. Assuming the standard deviations are reasonable and your studies are reproducible, you would want to exclude anyone out in that 2.5 percent tail, and I went ahead and just listed the values as they would range from age 20 at about 2,700 going down to 2,400 or so by age 60. That's sort of one way of looking at it.

The other way to look at it would be the way that the FDA has approached it. Look at do you have enough cells to make it near the age of death? And that's the other way to look at it.

In reviewing the FDA Attachment B, the threshold values selected don't exactly -- they do not likely allow a patient to undergo a secondary ocular procedure such as cataract surgery or further phakic IOL manipulation during the life of the patient. I would have concerns as a clinician if a patient had a cell count of 1,000 with a moderately dense cataract doing a phaco procedure. I have to be worried that I might tip them over into clinical corneal edema.

So I think we have to understand that the chart values selected, and I selected 1,500 and the FDA selected 1,200 and 1,000, are variable depending upon what our expectations are for these patients to have elective

procedures down the road, and it's impossible to precisely determine the minimum entry requirements without knowing the exact rate of endothelial cell loss per year at the various sites that run these. So when we discuss that particular table, I'm certain all those issues will come into play.

The issue that I haven't addressed, and I'll leave it to the statisticians, is regarding sample size analysis. Drs. Edelhauser and Bernie McCarey talked about that in the best case scenario, the best precision they can get on endothelial cell measurements is 2 percent and real-world data is at 9 percent according to Dr. McCarey. I wold like to know how that translates into the standard deviation values that our statisticians have calculated regarding sample sizes, if that's known, to see what kind of numbers we would actually need if we wanted to screen for the lower rates of annualized loss.

That would conclude my introductory comments at this time.

DR. WEISS: Thank you very much for a very thorough, as usual, presentation.

DR. GRIMMETT: Thank you.

DR. WEISS: Dr. Matoba has a question. Then we'll go around.

DR. MATOBA: Mike, I might have missed this,

but when you did your calculations, did you assume any amount of cell loss from the actual surgery?

DR. GRIMMETT: Yes. I assumed a 10 percent instantaneous loss at the time of the surgery based on the (inaudible) of having 8.8 percent with a phaco procedure.

DR. WEISS: Mr. McCarley, did you have a question?

MR. McCARLEY: I just had a couple of questions. The 9 percent that you're referring to is what Dr. Edelhauser and Dr. McCarey were talking about? Weren't those the controlled laboratory percentages and not actual real data?

DR. GRIMMETT: I believe it was real data from a real study, but we could probably have Dr. McCarey answer it, but Dr. Edelhauser's number of 2 percent precision was sort of in the best of hands what is the best precision.

MR. McCARLEY: Right, exactly.

DR. GRIMMETT: And Dr. McCarey's number was in order to -- it might be better to have Dr. McCarey answer, but I believe it was real data. I'm not sure how many eyes were in the study.

DR. WEISS: You can over there. As I recall, it was different centers, with the variation 9 percent between different people reading the same thing.

DR. McCAREY: Yes, it was real data from a

clinical trial that Medennium's working. It's the control data. There were 58 patients, seven clinical sites. I just started to collect the data and asked the question and came up with that answer.

MR. McCARLEY: Okay. I wonder is the FDA able to provide the panel, especially the voting members and reviewers, with data that they currently have on phakic intraocular lenses. In order words, the endothelial cell data that has come already out of the studies? There must be over 2,000 implants so far over --

MR. WHIPPLE: You mean the ones that are under IDE?

MR. McCARLEY: Pardon?

MR. WHIPPLE: Dave Whipple. You mean the ones that are already under IDE?

MR. McCARLEY: Yes, correct.

MR. WHIPPLE: We can summarize it.

MR. McCARLEY: In other words, we're reviewing the literature and making decisions based on the literature, and a lot of these have been recognized as being small studies. We don't know what methodology was used to validate -- the validity of the methodology and so forth. A lot of reference goes back to original studies that are even from the 1970s, from Bourne and group, and of course, he did a later study, but he did longitudinal study

showing I think 10 years' follow-up.

But I'd be curious, one, is can the FDA provide the panel members with the data that they have now to show them what the standard deviation is right now?

MR. WHIPPLE: Yes. They're special government employees. As long as they kept it amongst themselves, they could use it, yes.

MR. McCARLEY: Right. I would just say before a recommendation is made on limits and so forth, I would say you have real-time data, real data on real phakic intraocular lenses, that is up to date that you may want to consider before you make a final recommendation.

DR. WEISS: Well, actually, the advantage of this sort of meeting is that everyone's entitled to their opinion, there is no final vote, and there has to be consensus. So basically, the FDA will use all the information gathered here today, and including any other information we think would be helpful to obtain in the future, to come up with some final recommendations on their own.

Dr. Grimmett?

DR. GRIMMETT: Yes. Michael Grimmett. I alluded to it in my introductory comments that while it would be wonderful to have the Phase III endothelial cell loss data versus what is published in the literature, we're

not trying to set a threshold rate of what is acceptable to this panel or what is not acceptable. That's not even the purpose of this. But I approached the analysis in that fashion to show what the edges of the approach would be, so that we can get some data on how many patients would we need to screen in that range. That was my goal.

Understandably, the literature is not giving us that much guidance regarding actual cell loss rates because most of the lens designs have been just started and we're now on the newer lens designs. So we actually don't know what the newer loss rates are.

DR. WEISS: Dr. Mathers?

DR. MATHERS: Yes, I want to compliment Dr. Grimmett on his excellent analysis, and it may sound like it is rather strict, but I don't think that using the actuarial tables as you have is in any way offbase. In fact, it's probably ultraconservative because, as we have seen, as medical advances continue, it isn't impossible to look at ages beyond what you are saying, and we all know a lot of 80-year-olds who do not feel like dying right now.

(Laughter.)

DR. MATHERS: And who are probably going to live longer as these issues become more relevant. So 10 years from now, with one advance in cardiac pathology, this would become not strict enough.

I would also like to ask who you think should do the reading and the entrance qualification to get into a study like this, because clearly the endothelium, which is actually quite accessible as the cell to study, can be best read perhaps by a central office, and should the entrance requirements be that a central group does the initial reading to get in? What would you think of that?

DR. GRIMMETT: Michael Grimmett. Based on the comments of Dr. Edelhauser, given all the variability that exists if the technician is not trained properly and all the parameters to be analyzed, I obviously am in favor of the highest trained, highest precision measurer because of the critical nature of endothelial cell loss over time as our population ages.

DR. MATHERS: It wouldn't be difficult to do this with digital capture. You can transfer these images instantaneously and you can then decide whether you have good images, because it would seem that a lot of this depends upon having good images to start, so that you know how to get good data afterwards, and that's certainly possible on an instantaneous basis.

DR. WEISS: The way the document reads at the present time is that "The use of a reading center is strongly recommended. If the use of a reading center is not possible, the sponsor should establish a protocol for

collection and analysis of images to be used by each participating site."

Would you then change it from strongly recommended to required or you'd leave it as strongly recommended?

DR. GRIMMETT: This is Michael Grimmett again. I think there are always multiple ways to skin a cat, and if a particular study or a sponsor can demonstrate the reliability that they have internal mechanisms to validate precision and validity and it appears to be equivalent to a standardized reading center, I think there is always flexibility in that regard.

DR. WEISS: Dr. Huang?

DR. HUANG: My first comment is that regarding Mr. McCarley's comment earlier, using the FDA existing data is almost like using the soccer player to be the referee. You know, that we are judging the safety of the data and then using the data to be the reference for its own safety. I think it's questionable.

The second comment I would like to make is also that Dr. Grimmett used a very nice life table actuary to analyze this, but I think the endpoint is a little bit strict because we don't do cataract surgery at the time of the death. We do that cataract surgery maybe hopefully five or 10 years before the patient's life expectancy in

order to improve their quality of life.

So maybe we have two points that we can use. You know, maybe one at one point is 10 years before death and then at the death point, and then to find a reasonable middle ground for the starting point.

DR. GRIMMETT: This is Michael Grimmett again. Just a quick response. I first attempted to do the cataract surgical procedure 10 years before the age of death with an increased rate of annual cell loss. The table became so complicated in the formula that I would have to do to change the rate of cell loss midstream and back-calculate to the entry cell data that I couldn't get the spreadsheet to work in that regard.

I took took the give-up approach. You know, I was on vacation.

(Laughter.)

DR. WEISS: Well, maybe in that case, the guidance could be to the FDA to recalculate this with the average age of cataract surgery as the final.

Yes, Dr. Huang?

DR. HUANG: I'm just joking. I say, you know, maybe he can take another vacation to calculate that.

(Laughter.)

DR. WEISS: Dr. Burns?

DR. BURNS: Yes, but I think all things being

equal, if you move the cataract surgery earlier, you're going to actually end up with stricter numbers because you'll have the loss from the surgery and then you'll have an increased growth and you're going to come lower on the curve. So I think that will only make things stricter.

DR. HUANG: Andrew Huang again. I think this is just a recommendation. Not all the patients eventually are going to need cataract surgery, but I certainly understand that there will be additional loss, and I don't know which one is greater, 2 percent annual loss versus the 10 percent initial loss. So statistics will tell us.

DR. WEISS: I think it would be up to the FDA to crunch the numbers both ways to see what the differences are and if they're clinically relevant or not.

Dr. Grimmett?

DR. GRIMMETT: I would just point out on the tables, you realize that it is a 10 percent initial loss for the phakic IOL surgery. Please realize there are some data on some of the more current studies that say that that initial loss may at that rate, 5 to 6 percent. The earlier studies did have a higher rate.

So I used a cataract surgery phacoemulsification initial rate that may not exactly be true for phakic IOLs. I used the most conservative approach to make sure that we leave people with enough

cells at the end.

DR. WEISS: While we're on the endothelial cell topic, I just want to pose one other question relating to this, and then perhaps Ms. Lochner could come up and then we can go on with our other presenters and other discussions.

The other question that I would pose to the panel, as I already did to our experts, is what would you think would be the reasonable number of months to tell a patient they would have to be out of contact lenses? If you have an opinion.

Dr. Bullimore?

DR. BULLIMORE: None. I mean, I think keeping it --

DR. WEISS: Not even a week?

DR. BULLIMORE: Well, let me say less than a month.

DR. WEISS: Less than a month.

DR. BULLIMORE: I mean, I think trying to sort of take them out of contact lenses with the expectation that the endothelium's going to change in any meaningful fashion, based on my experience and what I heard from the experts today, is futile.

DR. WEISS: So you would keep them out long enough to get a proper keratometry or corneal topography?

DR. BULLIMORE: I mean, I'd use the same guidelines that exist for corneal refractive surgery.

DR. WEISS: Gee, I think we just eliminated two questions with that comment.

Dr. Mathers?

DR. MATHERS: Yes, I strongly agree with that. Aside from the fact that it would be really difficult to have patients go through that period of time, since the polymegethism afterwards doesn't really evolve very quickly and we don't know exactly the significance of it, I think that it's not terribly relevant to have them out of their lenses a long period of time, except to establish their refractive error issue.

DR. WEISS: Dr. Bullimore?

DR. BULLIMORE: And I think we need to be generalizable, and these products and these procedures are going to be done on people who, to a large extent, are long-term contact lens wearers. We saw yesterday that something like 80 to 90 percent of the patients enrolled in a study for low myopia or low to moderate myopia were contact lens wearers. So in the high group, it's going to be probably even higher.

DR. WEISS: Another question, which I warn you in advance I'm going to limit the discussion on because it will come up again, is with this in mind, would you only

want one eye done at a time or one eye done and use the other eye as a control for the endothelial cell study?

Dr. Bullimore?

DR. BULLIMORE: Again, I think you don't want to burden the patients too much, and enrolling them in, say, a three-year study where they can only have one eye done with a device and the other eye has to wait I think is an unreasonable burden to be placed on the patient. We have a lot of historical control data. It seems to me we have some historical data on endothelial cell count as a function of age. We can use that, and what we're looking for, I guess, are the extreme or the worst cases where people really do loss a lot of endothelial cells within a relatively short amount of time, and I don't think we need a control group to necessarily look at those event rates.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. My concern with a unilateral one-eye study would be for quality of life for the patient. These patients would be typically those that don't qualify for other refractive procedures, and hence they have a higher range of myopia. There is significant (inaudible) of emmetropia. So in a three-year duration study, I think that would be unwieldy and probably not very reasonable for the patient. So I'm in agreement with Dr. Bullimore.

DR. WEISS: Dr. Mathers?

DR. MATHERS: Yes, I'm also highly in agreement. I think we'll need to discuss again the time delay between the first and second operation, but three years is too long.

DR. WEISS: Then I would sort of conclude -- Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Yes, just very briefly. You know, statistically, we'd obviously like to have a contralateral, but I am absolutely swayed by the quality of life considerations as long as we have good quality control data. So that would include both a precise estimate of the rate of loss, but also of the variability in rates.

DR. WEISS: Okay. So then I would conclude that the fact that the contact lens issue in terms of the change and shape of the cells and number of the cells might still be evolving after the implant was placed in will be a confounding variable, but not objectionable by the panel. Fine.

Ms. Lochner, perhaps we can go on.

MS. LOCHNER: For analysis of the crystalline lens for lens opacity, we currently recommend that "The natural lens should be evaluated preoperatively and at each of the postoperative intervals. The level of evaluation should be commensurate with the risk of cataractogenesis or

lens changes identified by the risk analysis performed by the manufacturer. For phakic IOLs where the design or surgical procedure may lead to lens changes, a grading system or quantitative method should be used to evaluate lens changes over time. For IOLs for which lens changes are not an identified risk, qualitative observation may be adequate."

The analyses should include the number of patients with any change in the appearance of the lens stratified by the type of change and the number of patients with clinically significant lens opacities, and the term "clinically significant" is as yet undefined.

We are asking for panel comments on whether you believe evaluation of lens changes should be requested of all sponsors or whether this evaluation should only be performed if the sponsor's risk analysis warrants and whether you have any specific recommendations for defining the term "clinically significant" lens opacities.

We're also asking for your recommendations about the use of quantitative methods for measurements of lens changes versus the use of grading systems, and finally we'd like your thoughts on the duration of the study and request that you specifically discuss the length of follow-up you believe would be adequate for panel review of this cataractogenesis outcome.

Now, Dr. Mathers will provide his review.

DR. MATHERS: Thank you.

Regarding the first question we are asked to address, the evaluation of the lens changes, it is this reviewer's opinion that all phakic IOLs need to be evaluated for any cataract or changes in the lens. Anything that happens essentially inside the anterior chamber in front of the lens is an issue here, and even something that would not touch the lens or is known to be touching the lens would still be a problem. Certainly, central touch is not the only issue nor is just peripheral touch. There's anterior chamber inflammation, and all of this can affect the lens changes over time. So any perturbation would be of interest and all cataract processes need to be assessed.

In this direction, I think it's going to be important not just to look at the lens itself, but to look at the source of the possible problem, such as we have heard regarding flare assessment or anterior chamber inflammation, and I think that it would useful to measure flare in these patients with perhaps the laser flare system, and also, regarding the evaluation of the cataract process, that the sizing and the structure of the anterior chamber is going to be a key issue. So the use of high-resolution ultrasound I think is going to be extremely

important in evaluating this.

Regarding the clinical significance of the lens opacities, this is a more subjective area and we don't have very good data on this, but this of course refers to vision changes, and in this regard we need I think to be as precise as possible because when one measures vision under various circumstances, you get very, very different results.

So if you have a central opacification of the anterior subcapsular area, it will not show up in vision testing in a dim room. You're going to have to do this with a small pupil under conditions that will induce some glare, and in fact, the more glare, the better. This is not a non-real-life situation. I mean, when people are in a high-light environment, which they often are, this comes into play.

So I think glare testing is the most relevant, but the only way that this should be assessed. For this, we need to have careful measurements of the patients as they enter the study and a standardized method of evaluating the glare, and that high-glare settings should be used.

Now, everyone will have some decrease in visual acuity with a high setting of a glare. So we have to decide whether we think one, two, or more lines of loss

compared with the preoperative evaluation would be significant. My recommendation would be two or more lines compared with what they had in the loss before.

I think that all lens changes should be reported, not just the anterior subcapsular fibrosis, but we also have anterior cortical changes which may result from these anterior subcapsular processes.

The posterior subcapsular cataract is also an issue because the anterior lens cells are not the only ones going to be involved. As you build lenses that do not ride or touch the central lens, they may ride in the periphery of the lens, and they are going to get closer to those cells on the outside which can migrate posteriorally, and certainly may do so. So that becomes an issue, and the possibility of inflammation that occurs with the anterior chamber lens of this design may affect the development of nuclear sclerosis, and this is going to be something that is going to be harder to assess, but I think that we need to at least monitor this.

In Part C, we're asked to comment on the use of quantitative measures for the measurement of lens changes versus the more semi-quantitative grading system, and by quantitative here, we mean the assessment or the visualization, the optical visualization, of the changes underneath the anterior capsule.

There is no standard way to do this and the examination of this is very light-dependent. If the lighting system is a little bit off, you get a little different view of this and it becomes harder to see, and Dr. Werner's presentation on this was excellent, but even she could not really tell us exactly how much better, say, a photographic system is from a slit lamp system, which of course is going to be subjective. But I believe that the backlighting and retroillumination of the lens with high-resolution color photography probably offers us the most objective and reliable way to follow this over time.

The development of a scale to do this has already been done. I don't think this needs to be reinvented, but can be perhaps modified slightly. The LSCS system can grade these opacifications and can be used for all of this -- the anterior subcapsular, the posterior subcapsular, and the nuclear -- and I think something like that would be appropriate.

I would strongly recommend the use of digital photography to perform this process and I also think it is possible, as technology improves, that we will have a better understanding through other means of visualization, perhaps confocal microscopy of these cells now that this becomes an issue and it becomes relevant to look at this. But there are no standards for this now, and that would not

necessarily be used in an early study like this.

In Part D, we're asked to comment on phakic IOLs and the length of time that it might be useful to evaluate this for, and here, as we've heard with the endothelium, when we're studying the endothelium, we have a fairly clear endpoint. We have endothelial cell loss and we can follow this fairly objectively.

With lens changes, it's much less objective, and one study, noted recently, showed that there was some change in light transmittance with these lenses, not necessarily based on cataract, but I think that with the long time span that we're talking about and the possibility of chronic inflammation associated with this that is subclinical, that at least three years would be necessary to evaluate it. I think that the monitoring of this perhaps should go on longer than that, but I think the three years is probably enough to give us an idea of what is happening.

The capsular process of cataract formation is tied to a number of different other processes. Not just lens touch, but, as I said, inflammation, and as the lens is redesigned to minimize the cataract process, the other issues, such as iris touch and development of pigment dispersion and glaucoma, become more of an issue, and I think that the industry or lens manufacturers will be

tempted to avoid the obvious problems of lens touch by then shifting the burden to the back of the iris. I think that this kind of monitoring is also going to be important. I know it's not part of this particular issue, but I think it's relevant because there are tradeoffs here. There is not much space in this area and as you design the lens to perform in one way, you then create other issues of significance.

That is my summary.

DR. WEISS: Thank you very much.

I just have just two questions on things which you've already mentioned, but I just want to clarify. What would you call a clinically significant cataract?

DR. MATHERS: Clinically significant cataract refers to a loss of a number of lines, but it's highly dependent upon that is assessed, and I think that needs to be assessed not just with standard -- well, our assessment of vision can be done in the standard way in dimly lit room to optimize vision, but it needs to go beyond that. We need to have glare testing as well because our standard measures of vision will not be adequate to pick up the kind of changes we're going to see with capsular opacification.

DR. WEISS: So then to just restate that, with glare testing, it depends on sensitive you want to be to a very early cataract, and that's the question I'm asking, is

how sensitive do you want to be? So if we said let's it bring it to the glare testing realm and say, okay, we're going to determine that by a loss of X number of lines by glare testing, is there an idea you have?

DR. MATHERS: Certainly, it has to be more than one line, so I would say two.

DR. WEISS: So would you prefer, if I was going to make you quantify it, would you then say a loss of two lines by glare testing, rather than just a straight loss of two lines without the glare testing or would you want to say something else or it's totally unknown?

DR. MATHERS: I think without the glare testing loss of one line would be important, would be significant. With glare testing, it's going to be two, because the glare testing is much more sensitive.

DR. WEISS: And would you require contrast sensitivity data or that would be optional?

DR. MATHERS: I think contrast sensitivity data also should be included.

DR. WEISS: Okay. So you'd like to have both, but at least at this point of the discussion, a loss of two lines at glare testing would be considered significant.

Dr. Bradley?

DR. BRADLEY: Yes, just a comment on the means by which one does glare testing and how that interacts with

the underlying spatial distribution of the cataract. We might think of two scenarios, one that was just mentioned of a central cataract that is anterior or posterior. The idea of most glare testing is you employ a bright light source and, in so doing, the pupil constricts, and therefore the cataract fills a larger proportion of the pupil, and therefore the scattered light becomes a larger proportion of the retinal image, and that leads to an increased visual effect.

Obviously, the converse is true. If you have a peripheral or marginal cataract, as the pupil is constricted, a smaller and smaller proportion of the pupil is covered by the cataract, and therefore a smaller proportion of the retinal image is scattered light, and thus the visual effects are decreased under those circumstances.

So I'm not sure there is a single way one can do a glare test that would sensitize the tester to the visual impact of a cataract, and it may be necessary to employ more than one approach. Just an off-the-cuff suggestion would be to employ the one suggested, which is the standard approach, perhaps, where the pupil constricts in the presence of the bright light and it's highly sensitive for picking up the visual impact of a central cataract. I might also suggest performing the same test

under cycloplegic pupil dilation to emphasize the impact of a marginal or peripheral cataract that, of course, would be visual manifest for the patient under, for example, night driving circumstances, which arguably are the most important ones.

DR. WEISS: The question, Arthur, has anyone done cycloplegic glare testing? Do we have any data to know what the results are in the normals?

DR. BRADLEY: I don't know.

DR. WEISS: Dr. Mathers?

DR. MATHERS: I would strongly agree with what you have suggested. I meant that we should do standard testing, contrast sensitivity testing, and glare testing, and I do not have any experience doing glare testing in a dilated pupil, but it is similar to night driving, but we just don't have any data on that, and I don't think that the visual assessment is going to give us all of the answer. I think we're going to see a lot more with the objective and quantitative than we do simply with the vision changes.

DR. WEISS: Well, perhaps if we don't have that data, we could request a subset. If panel thought that was helpful and so did the agency, we could request a subset of patients when they have their initial entry dilated exam to be glare tested while dilated and not dilated, so not to be

too onerous to any sponsors.

Dr. Grimmett, then Dr. Bullimore.

DR. GRIMMETT: Dr. Grimmett. Just a quick comment. If my memory serves me correctly, I think I've seen some dilated glare testing data in an ARVO abstract by Arthur Ginsberg out of California, San Ramon. He does functional driving tests and other activities and has some data on that kind of stuff. He's a contrast sensitivity guru. I think I've seen that data before, so I think it could exist.

DR. WEISS: Dr. Bullimore?

DR. BULLIMORE: My impression is we're going to come to contrast sensitivity in a minute and glare testing, but since it's on the table, this is a real sticky area, and anybody who a few years ago was involved in the Eye Care Technology Forum knows that agreement was quickly reached on some areas, like measurement of intraocular pressure and visual acuity and visual fields, but contrast sensitivity and glare testing became a thorn in the side of the organizers of that meeting, and Morris Waxler was the point person on that and Arthur was involved in the panel as well. It was very difficult.

As far as assessment of cataract, I think one of our speakers put forward a number of mechanisms by which a standardized grading system could be used. I think the

panel should consider whether the FDA should strongly recommend a reading center for cataracts or for lens opacities in the same way they're recommending it for endothelial cell density.

It becomes difficult because in the case of endothelial cell density, you have a standardized instrument that can capture the image. Photographing lens opacity, since you want to capture the different features of the lens, is a much more difficult and sophisticated procedure.

So I think using standardized grading systems is appropriate, paying attention to the kind of opacities that are likely to occur. Anterior and posterior capsular opacities I think are appropriate, and cortical opacities maybe, but I'm not in favor of requiring a reading center in the same way that it's currently recommended for the endothelium.

DR. WEISS: If there are no other comments on this section, Ms. Lochner, if we could proceed to the third and last question.

MS. LOCHNER: At the most recent ANSI meetings, a consensus appeared to be reached on the general parameters of the contrast sensitivity substudy that's outlined in Section 8.3, and Dr. Bullimore, you might be interested to know that we had Dr. Ginsberg, who's the

contrast sensitivity guru, and we had Dr. Jack Holiday, who's advocated contrast acuity testing, actually agreeing on this point. So it was a red letter day.

(Laughter.)

DR. BULLIMORE: For the record, I never called him a contrast sensitivity guru. That was Dr. Grimmett. I want to strictly go on the record on that.

(Laughter.)

MS. LOCHNER: And I think that the use of the contrast sensitivity systems, rather than contrast acuity, was recommended because of contrast sensitivity's ability to capture the full range of spatial frequencies and contrasts, and it was felt that the contrast acuity charts would potentially miss significant contrast losses because of the unpredictability of the spatial frequency at which these losses may be seen. Of course, we will have letter recognition performance under low light conditions assessed by the best-corrected visual acuity testing.

The contrast sensitivity testing, as proposed, includes mesopic and mesopic with glare conditions. Please comment on the clinically significant decrease being set at .3 log units, and also on whether this decrease should be at one or two or more spatial frequencies to be considered significant.

Next, should charts with the minimum contrast

at each spatial frequency be used to minimize the problem of missing data, and perhaps first of all, are these charts commercially available?

Please also comment on the recommended analyses of these data, including how missing data should be handled, and by missing data, we mean when the patient is unable to see the target at a particular spatial frequency at any of the available contrast levels.

Last, please provide any additional comments, particularly any recommendations you may have to improve the quality of the data generated from this testing.

Dr. Bullimore?

DR. BULLIMORE: Can you go back to the first slide? I want to take these questions one at a time with panel input, if that's okay, Madam Chairman.

DR. WEISS: Anything you want.

DR. BULLIMORE: Wow. I guess lunch is not on the table.

(Laughter.)

DR. WEISS: That's true.

DR. BULLIMORE: Let me paraphrase my comments by saying that I have a long and distinguished record of being a fan of letter charts over grating, so anything I say should be taken in that context.

That notwithstanding, I think first of all, the

statement about .3 log units being a clinically significant decrease in contrast sensitivity is reasonable. Just to put that in context, we've come to accept two lines of visual acuity on a logMAR chart as being a meaningful decrease and representing a complication or an adverse event or, to put it more broadly, an unsatisfactory outcome of a refractive procedure. Here, we're talking in the contrast domain of an equivalent of three lines, and I think this is reasonable and conservative.

I think saying that the drop should be at two or more spatial frequencies, again, we get into the martial end of contrast sensitivity testing pretty quickly. One of the limitations and reservations that some people have about these tests is that unlike letter testing, for example, where the patient has to name a letter, the patients is asked either whether they can actually see the grating or not or is asked to say is the grating on the top part of the chart or on the bottom part of the chart? So the opportunity for a bias based on shifts in criteria if you use the first approach or the opportunity to sort of guess correctly when it's just a one in two chance compound the analysis of some of these data.

But again, in the interests of the goodwill exhibited between Dr. Holiday and Dr. Ginsberg, I think this again is a reasonable, practical approach, and with a

letter chart, of course, you might not have the problem with then having to say, well, is it one or two spatial frequencies, but really I think the panel at this stage should be presented with the data when it's available and let the panel decide, so to speak.

Does anyone want to comment on that first thing? I'm sure Arthur would. I'd appreciate Dr. Owsley's input anytime she wants to say something.

DR. WEISS: Dr. Bradley? Or Owsley. Whoever.

DR. OWSLEY: Why don't keep going and then I can probably just make a few comments at the end?

DR. BULLIMORE: Okay. Arthur, can I keep going for you as well or do you want to interject?

DR. BRADLEY: I really appreciate the opportunity to interject.

(Laughter.)

DR. WEISS: So why don't you?

DR. BRADLEY: Mark raises an interesting sort of comparative analysis to try and decide, well, is .3 log units, obviously a factor of two changing contrast sensitivity, clinically significant? And he draws the parallel between what people decide is clinically significant in terms of logMAR for visual acuity change, and two lines, obviously that's .2 log units on a logMAR chart, and I question, Mark, that that is somehow

equivalent to .3 log units in contrast sensitivity. Was the equivalence based upon some sort of Z score change, Mark, or --

DR. BULLIMORE: I didn't mean to imply that they were equivalent, but I said it sort of parallels the change.

Now, you could say, well, if we're doing .2 log units of visual acuity, we should use .2 log units for contrast sensitivity. Unfortunately, most of the commercially available tests for contrast sensitivity go in steps of .15.

Again, we're going to have the data. We're going to be able to look at the number of patients that have lost .3 or more log units at one or two spatial frequencies. We'll have mean contrast sensitivity data for each spatial frequency and for each lighting condition. There will be a colossal amount of data that we'll be able to sort of chew over in depth when the opportunity arises.

DR. BRADLEY: Yes, I think we'll have the data, but we'll still be left with the question about what's going to be significant.

Just as a suggestion, then, I would make that if there is consensus that a .2 log unit change of visual acuity is clinically significant, would you think it reasonable that we convert that into some sort of acuity Z

score change -- say, two, three, four standard deviations, whatever it is -- and propose that an equivalent Z score change in contrast sensitivity be considered significant. Does that make any sense at all?

DR. BULLIMORE: It makes sense, but I don't think it's an approach that I would advocate at this stage.

DR. WEISS: Dr. Owsley?

DR. OWSLEY: This is Cynthia Owsley. I think one of the --

(Telephone rings.)

DR. OWSLEY: Could somebody get that?

DR. BULLIMORE: I think it's Art's.

DR. WEISS: It's probably Pizza Hut returning someone's surreptitious call.

(Laughter.)

DR. OWSLEY: I mean, I think both Mark's approach and Arthur's approach are reasonable approaches. The problem for me, when I think about this, is when you decide how much decline on a visual function test is bad in some sense, clinically significant in a bad sense, you have to ask yourself what is it you're trying to prevent.

Answering these questions in vacuo without looking to see how much of a loss you need in contrast sensitivity or acuity or glare or whatever the visual field causes a problem in functional performance, without looking

at it in that way, I just don't see how you could answer the question.

I'm not suggesting that we propose all kinds of -- whatever they're called -- substudies to answer that, but I think it's an important dilemma, because when it's considered on its own, it's abstract. For the patient, it's in terms of their everyday life. What implications will a .2 loss in logMAR acuity mean? What implications for their everyday will be a .3 loss in contrast sensitivity?

So I haven't proposed any answers to this, but I see it as a very sticky dilemma that we might just have to kind of go with something that feels like it has some face validity sort of on a clinical level.

DR. WEISS: Mr. McCarley, Dr. Mathers, Dr. Bandeen-Roche, and then Dr. Bradley.

MR. McCARLEY: Yes, just one question. Is this the first time contrast sensitivity testing has been required by the panel? My understanding is that manufacturers of refractive lasers also collected this data. I mean, the question behind that is is there a standard for contrast sensitivity or are we now making the standard?

DR. WEISS: Well, we're making a standard for phakic IOLs, so even if it wasn't required for anything

else, it really --

MR. McCARLEY: In my understanding, it was. Maybe I'm wrong.

DR. WEISS: Well, I'll defer to Mr. Whipple.

MR. WHIPPLE: Yes, I believe we have required contrast sensitivity for LASIK studies.

DR. BULLIMORE: Yes, and the current guidance document says that either you have to measure it or basically to say that you didn't measure it.

MR. WHIPPLE: Right, and I'll defer also if Donna and Malvina --

PARTICIPANT: That sounds definitive.

DR. BULLIMORE: I'm paraphrasing a little bit, but that's the general spirit of it.

DR. WEISS: Donna?

MS. LOCHNER: Well, it's not the first time it's been required. As you point out, the LASIK example, and of course the panel has reviewed extensive contrast sensitivity data in the multifocal IOL example.

I think it's also important to point out this question about the clinical significance because I think what Dr. Bullimore was saying about, you know, you're going to have to look at the data and make some judgements when it's received, but this question is backing up to the sample size calculations. It's not backing up that if it's

.3, the device is approved and if it's .29, it isn't. It's really more is this a reasonable effect to be looking at the sample size calculations, et cetera.

I think also, as Dr. Owsley said, the meaning of this is really not going to be clear to many of the panel members, as well as to the patients, unless this were there were this daily living-type testing required, which we really have not -- we're not suggesting that, but I think it's a point well taken. So really, if you think of this in the context of the sample size.

DR. WEISS: I think Dr. Bullimore --

DR. BULLIMORE: Yes, I mean, you can look at a .3 loss as being clinically significant two ways, whether it occurs in a subset of individual patients or in one individual patient or whether it occurs in the population as a whole, and in terms of sample size, you're interested in the population as a whole. In terms of the safety of a device, you might say, well, if a two-line loss of visual acuity sets off alarm bells and appears on some summary statistics for safety, then should there be an equivalent here?

I'm not comfortable doing the later. You know, we heard from a speaker this morning who has a lot more experience with phakic IOLs than the rest of us, and he was advocating that the IOLs be held to the same standard

visually as LASIK, and we have some historical precedent here with these tests being done on everybody and I think we should carry on with that.

In terms of the sample size for the entire cohort, I think it's much more likely to be driven by endothelial cell density considerations than anything visual.

MS. LOCHNER: So it's your recommendation that this testing be performed on all individuals?

DR. BULLIMORE: Yes. That would be my recommendation.

DR. WEISS: I think we're going to go along this time even if it's out of order I originally said.

DR. BULLIMORE: I'm not asking that everybody flies to Iowa for a driving simulation. I mean, this a test that should be reasonably easy to incorporate into a protocol and I would like to see data on as many patients as possible.

MR. CALOGERO: Don Calogero. Right now, it's set up as a substudy, and I believe the sample size is somewhere between 60 and 100 patients, and that gives us the ability to detect down to .15 log units. So you're saying that in spite of perhaps having sufficient precision to the study, you'd like to see it on the entire population?

DR. BULLIMORE: Well, I think where Dr. Mathers was going with this is that he would like to see data on contrast sensitivity with and without glare that would give you clues, maybe not definitive decisions, as to whether significant cataractogenesis had occurred in these patients.

MR. CALOGERO: Okay. So you're also using it for that purpose, then.

DR. BULLIMORE: Exactly. Now, if my memory serves me correctly, I mean, yesterday's presentation for an intraocular --

DR. WEISS: Wavefront.

DR. BULLIMORE: Wavefront. That was it.

DR. WEISS: How quickly we forget.

DR. BULLIMORE: A good dinner.

For that, we had data on all the patients. Am I correct?

MR. CALOGERO: I believe so, yes.

DR. BULLIMORE: Yes. So I would have thought, with a newer technology, which, let's face it, these phakic IOLs are, and I think increased or elevated safety concerns in terms of lens opacities, I'd want to have that data on as many patients as possible.

Now, I realize we may be into latter phases of some PMA investigations, and that's fine, but I think it's

going to inform at this stage whether the patients have indeed developed anything that may cause concern in the lens opacity department.

MR. CALOGERO: Thanks for clarifying that.

DR. WEISS: Dr. Mathers, then Dr. Bradley, and we'll move our way around, and then come back to Dr. Owsley.

Dr. Mathers?

DR. MATHERS: Yes, I agree with Dr. Owsley that it's difficult to assess how this impacts the patient, but what we need to do is have reasonably high resolution of the data that we're picking up. When we're talking about whether this is actually a good thing, you have to contrast that with the struggles the patients have with enormous myopia and their tremendous problem and the alternative of clear lens extraction and other significant issues, but we want to have reasonable resolution and an ample sample size so that we can tell what's going on, and it may be that two or three lines is a reasonable expectation considering the other struggles that they have. But we would determine that later. We need to have the data now, and I think the contrast sensitivity not only gives us something about the visual function of the system, but also the cataractogenesis process.

DR. WEISS: I think that probably most people

here are in agreement that we need the data and whether or not someone postulates that they know what the data means upfront versus whether they don't know what the data means upfront really won't affect the FDA. They can just tell you after the fact whether you were right or not.

So if anyone has any comments not related to their opinion on that particular topic, we can proceed with them.

Dr. Bradley?

DR. BRADLEY: Yes, I think just because this is a new product doesn't necessarily mean we have to measure contrast sensitivity. We really need to have sort of underlying theoretical rationale for why contrast sensitivity measurement might or might not be useful in this particular case.

I think the primary concern we have here is degradation of optical quality, whether it be in the cornea due to endothelial problems or primarily in the lens due to cataract development. The likely optical and visual consequences of that are related to scattered light, and they have fairly predictable optical effects. Indeed, they will have some effect on our ability to see fine detail, which ought to be revealed by some visual resolution task.

In addition to that, they will have impact on the image quality for larger targets, and the primary

impact will be on contrast reduction. One method for assessing this is to examine contrast sensitivity.

That said, as Mark alluded earlier, there are devotees of letter contrast sensitivity testing and there are devotees of grating contrast sensitivity testing. One of the arguments in favor of grating testing is that one can test at many spatial frequencies, which academically might be quite interesting, but unless one can come up with a reasonable theoretical argument for why a measurement at a single low spatial frequency might not provide the same information, I think one is wasting one's time measuring at lots of different spatial frequencies.

Therefore, I wonder about most grating tests for that reason, and I think Dr. Owsley might be able to comment on that.

DR. OWSLEY: Yes. I very much agree with the perspective or the question you're raising. I would not describe myself as a devotee or a guru of any test.

The reason I favor letter tests in situations like this is that I know of no convincing evidence in the peer-reviewed literature that shows that letter tests are worse than grating tests or grating tests are better than letter tests, however you want to say it.

I think that there are a lot of us who do clinical studies, clinical intervention evaluation studies,

including bodies like the National Eye Institute, who go the way of letter tests not only based on the evidence that they're not worse than the grating tests, but because of two things. One, if you're getting a measure of high-resolution visual acuity, and then you do a contrast sensitivity letter test, say like the Pelly-Robson, which has large letters, you're basically getting information about the entire shape of the function.

Then the second reason is that we're talking about -- I don't know which specific test the sponsor would be using or any sponsor would be using, but if you're doing spatial frequency testing in the kinds of things we're talking about in this kind of study, you're doing those spatial frequencies for topically, mesopically, with glare and without glare, before and after surgery. This is a long testing time, okay?

And then I think -- what was my last point on this? Well, I'll just leave it like that, but I know that this issue has been visited by this panel before and I've heard about it. I've never been to the panel to hear it argued as a panel member, but I think that it's an important point that sponsors should hear, the public should hear, and the FDA should hear that there really are really sound arguments for not, in every case, doing all the spatial frequencies. You need to ask yourself, what

are you doing with that information? What's it really providing for you that high-contrast acuity in a single measure on a large letter contrast sensitivity chart would not provide?

DR. WEISS: Dr. Swanson?

DR. SWANSON: I agree with both sets of comments and wanted to add one other thing. I've used letters and spatial frequencies. It depends on what the task is.

The point that Dr. Bullimore raised becomes important for sample size calculations as well as for the amount of time that goes on, particularly if we're looking at this question of glare, but as Dr. Bradley mentioned, in general, these effects should be in a range of spatial frequencies.

If you are using a grating and you have a two-alternative forced choice, basic researchers who use those things do lots of trials because that's the only way you can reduce test/retest variability. For letter testing, where there's going to be between 10 and 26 options that the person's guessing amongst, a much smaller number of trials is needed.

So in order to have a significant change, you need to have a test where the test/retest variability is low. For a small number of trials, which needed to run all

these conditions in all these people, a multiple alternative, 10- or 20-alternative forced choice test, is going to be much better than a two-alternative forced choice, and there aren't any commercially available 10-alternative forced choice grating tests and it's going to be very difficult to create on given the response demands on the patients. So a letter type of acuity test is going to be much more suitable in terms of gathering a fair amount of useful data in a short period of time.

Then the questions that come up, such as, well, do we have to have two spatial frequencies down or three spatial frequencies or one spatial frequencies down, those become quite complicated by the high test/retest variability of a two-alternative forced choice with just a single endpoint.

DR. WEISS: So let me get to a bottom line. What do you want?

DR. SWANSON: I'm just trying to hammer home all the points they made about letter charts being superior for this purpose. I understand there was agreement before.

DR. WEISS: So you would like a letter chart for this purpose.

DR. SWANSON: For the purpose, a letter chart is going to allow a much smaller sample size and a much larger --

DR. WEISS: And Dr. Owsley, you agree, and Dr. Bradley?

DR. BRADLEY: Yes, I agree, a letter chart. I think Donna asked us if such charts were available. There certainly is a letter contrast sensitivity chart, as I think it's been referred to. Sometimes it's called a Pelly-Robson chart.

One thing I would alert the FDA to is if you are to request use of that chart, it doesn't have to be used at the standard distance at which it was originally designed, and there are reasons to pick your distance, depending upon the scale or size of target for which you wish to study.

DR. WEISS: Dr. Bullimore, your comment?

DR. BULLIMORE: I mean, the spirit in sort of guidance documents before, whether for this issue or others, was that the sponsor or a potential sponsor would be able to speak with the FDA and the FDA, in terms of the guidance document, wouldn't specify a given test, but there would be some scope. I was just a little surprised that this was so specific, even naming spatial frequencies. I mean, you come pretty close to naming a test or naming a couple of tests, and I'd just like to see some statement that other tests could be considered if the sponsor in consultation with the agency would be able to agree that

these were acceptable.

DR. WEISS: Don Calogero?

MR. CALOGERO: I can provide a little background. At the last ANSI meeting, we sort of discussed this issue, and there was a presentation and the basic summary of the presentation was that it's really not possible for us to predict where the largest effect is going to be in terms of the spatial frequencies. We went through the literature containing some information --

DR. BULLIMORE: But Don, the panel's telling you that that's not an appropriate -- well, not necessarily a widely held view of the world.

MR. CALOGERO: Well, this was from the literature and this is from sort of the internal data we have. Some devices, depending on the type, had the largest effect at 1.5 cycles per degree, others 12 cycles per degree, and the committee felt that if we had recommended the letter charts, based on sort of the spatial frequency domain that they evaluate, you're essentially just simply getting the highest spatial frequencies, maybe 12 cycles and above, whereas we could potentially miss large drops at other spatial frequencies, and with our current to predict where the effect is, we felt it would be judicious to recommend that the entire contrast sensitivity function be defined.

DR. OWSLEY: Can I make a comment?

DR. WEISS: Yes. Make a comment, Cynthia, and then also if we could direct it at, from what I understand from the vision scientists on this panel, they don't agree, and is that the case or is that not the case?

DR. OWSLEY: The vision scientists on this panel I think do agree the letters would be better.

DR. WEISS: No, you agree that letters would be better, but are you agreeing with what's been put forward by the FDA?

DR. OWSLEY: Well, let me put it like this.

DR. WEISS: That's what I'm asking.

DR. OWSLEY: And that's exactly what my comment is on. I've been reading this literature for 20, 25 years, like Arthur -- Mark's a little younger -- and Steve.

DR. WEISS: He's thinking a lot younger.

DR. OWSLEY: I would be happy as a consultant to the panel to look at those peer-reviewed papers. Of course, if you have internal data you can or cannot share with me, that's your decision, but I have not seen any convincing evidence that measuring all these different spatial frequencies would matter in any of the decisions that you would be faced with at the FDA regarding these types of devices. But I'm openminded. I just haven't seen those papers.

DR. WEISS: So I see sort of agreement by Dr. Swanson.

Dr. Burns has a comment.

DR. BULLIMORE: I mean, my overall view is that these --

DR. WEISS: Dr. Burns has a comment.

(Laughter.)

DR. BULLIMORE: This --

DR. WEISS: Well, I guess Dr. Bullimore has a comment.

(Laughter.)

DR. BULLIMORE: Since it's my --

DR. WEISS: Dr. Burns is deferring to you, Mark, so why don't you give your comment?

DR. BULLIMORE: I have no problem with gratings being used. It was just having a sentence in there that other avenues could be pursued if --

DR. WEISS: So you don't like the rigidity of it, but you don't have a --

DR. BULLIMORE: It's more the rigidity, and I mean, as I said before, you're almost sort of saying you've got to use this test or this test, and those of us who work in other arenas, and we've already spoken about the limitations of certain types of tests, we just find that a little offensive, I think.

DR. WEISS: Dr. Burns, and then Karen Bandeen-Roche and Mr. McCarley.

DR. BURNS: Yes, I just want to chime in that I also believe that the combination of the high contrast and the low contrast letter chart will give us enough sensitivity both for some of the safety issues, such as contrast degradation from cataracts combined with glare, and remember also, this is a refractive procedure. So we do want to get general decrement information. But I do believe that a contrast letter chart combined with a high contrast letter chart will be acceptable.

DR. WEISS: Mr. Whipple?

MR. WHIPPLE: Yes, Dave Whipple. I just wanted to address Mark's comment about the rigidity of the guidance. We may recommend certain tests or prefer certain things, but a guidance is exactly that. It's guidance. It always carries with it the option of using other tests, other test methods, and making arguments why the recommended tests aren't appropriate for that particular device. So that's inherently built into the guidance document development.

DR. WEISS: We'll go on to the other two comments if they're not related or they don't change what my next statement is going to be. It's from why I understand, the members of the panel prefer a letter chart

and Dr. Bullimore would also prefer that the wording doesn't sound so restrictive, even if it actually isn't.

Having said that, do you have anything else to add to that, Dr. Bandeen-Roche or Mr. McCarley?

DR. BANDEEN-ROCHE: My comment was a brief one on a different topic, so should we finish this?

DR. WEISS: If it's related to this question --

DR. BANDEEN-ROCHE: It's related to clinical significance in terms of functional performance.

DR. WEISS: Well, why don't you just proceed?

DR. BANDEEN-ROCHE: I just wanted to mention that there is detailed data from the Salisbury Eye Evaluation Project on glare, contrast, et cetera, with many measures of functional performance. So I don't think we're completely in the dark. I think that there are some data that can inform that question, albeit it is a sample of older adults.

DR. WEISS: Good. Thank you.

Mr. McCarley?

MR. McCARLEY: Yes, just very quickly. I'd like to understand or get clarified for me the intent. My understanding, at least from the ANSI side of it when we've been discussing this for the last several years, was that doing contrast sensitivity was to see if the combination of optical components in the eye degraded, similar to what the

intent was when they did LASIK studies. Now, it seems to be that's what's being used to determine whether or not the patient's undergoing a degradation as a result of cataract, for instance. So one would be a sample size and one would be all patients, I think.

DR. WEISS: Dr. Bullimore, did you want to address that?

DR. BULLIMORE: No.

DR. WEISS: No one wants to address that. I guess we have no takers?

DR. BURNS: If you're measuring a visual performance like this, you're tapping the whole system, and the degradation can come about from optical imperfections or from what are actually just very high-order optical imperfections of scattering and tissue turbidity. So it probes the whole system.

DR. WEISS: I think we've beat this one into the ground and it's no longer even gasping. So why don't we go on to the next one?

DR. BULLIMORE: The next one I think is very easy to deal with.

DR. WEISS: We'll hold you to that.

DR. BULLIMORE: Again, we're asking people to be very specific about the tests, and I think the FDA have enough savvy and flexibility to deal with this, but if

somebody can't read or can't see the highest contrast on the chart, I think their contrast sensitivity has to be scored as zero. One would hope that preoperatively the test was sufficiently intelligently designed such that they could read well above that bottom level.

Certainly, recalling some of the data we were presented with yesterday, we were dealing with contrast sensitivities of one or above most spatial frequencies. So as long as we have something down at the 40 percent or 60 percent, which of course is .3 or so contrast sensitivity, we should be okay.

But if they can't see it, it shouldn't be counted as missing data. We should assume that their contrast sensitivity is zero or some other intelligent value based on the range of the test.

DR. WEISS: So can the transcript reflect there are about six heads bobbing up and down?

Next question.

DR. BULLIMORE: And the next question, please, Donna?

I think this is kind of tied in with the last one. If I can answer, I think tests are available and if a patient can't see a targeted spatial frequency at any contrast, it should be scored as a contrast sensitivity of zero.

MR. WHIPPLE: That is information.

DR. WEISS: Dr. Bradley, and then Dr. Swanson.

DR. BRADLEY: I'm having a bit of trouble with the question. I mean, we're not anticipating these patients are going to have horrible vision, are we?

DR. WEISS: Before or after the implant?

(Laughter.)

DR. WEISS: Sorry.

DR. BRADLEY: I mean, we're talking about some serious methodology here. We're trying to ascertain something fairly subtle, and I don't think in any of these cases we're going to have the problem that people can't see the target at all.

MR. CALOGERO: I think why we're asking the question is under the mesopic test conditions. Under the mesopic test conditions, we do in fact have cases where at the higher spatial frequencies, the patients are unable to perform anything, and so you might have 20 or 30 percent of the population that you're testing that essentially has a zero, let's say, 12 or 18 cycles per degree. So we wanted some sort of standardized way of handling all of those zero data points.

DR. BRADLEY: Well, I think the panel has given you our suggestion on that, which is that you should not do these grating tests. Particularly, don't try to find out

if people can see fine detail in the dark. We know they can't.

DR. OWSLEY: This is Cynthia Owsley. It's very unusual to find a patient who can't see the first triplet of the Pelly-Robson chart, and I see Karen Bandeen-Roche from the SEE Project nodding.

DR. WEISS: But in that case, I think we have the answer to this question. We may not like the question, but I think Dr. Bullimore has already given an answer to it, which I assume you would agree to, but you don't think it's going to even come up.

Fine. Next?

DR. BULLIMORE: Beaten to death. Beaten to death.

I really have nothing to add on this one at the moment. I'll read it again. "Please provide any additional comments on the contrast sensitivity substudy" -- now it's a substudy -- "including any other guidance that could be provided to enhance the quality of the data that are generated from this testing."

Use a good test would be my recommendation.

(Laughter.)

DR. WEISS: That's why we call the experts to figure this out.

DR. BULLIMORE: And use it well.

DR. WEISS: So is that the end of your questions?

DR. BULLIMORE: I'd like to hear what Dr. Owsley has to say.

DR. WEISS: Dr. Owsley?

DR. OWSLEY: I think the test should have the best test/retest reliability as possible and should be brief.

DR. WEISS: And brief is always dear to my heart.

Yes?

DR. BULLIMORE: This is Dr. Bullimore again, not wanting to shut up. I think it would be ideal and preferable and maybe mandatory that for any test that's going to be used that normal data are available on a wide range of age ranges and for the measured conditions.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: I think just to reiterate what everybody has said here and maybe to put the comment that Bill Swanson made earlier, what we're arguing for regarding the quality of a contrast sensitivity test can be thought of by thinking of an analogy with a visual acuity test.

Imagine you had a visual acuity chart, one letter per line, and it was either A or B. Would we consider that an appropriate test? And clearly not, and

all we're saying is let's hold the contrast sensitivity test to a similar standard psychophysically in terms of rigor and test/retest reliability that we are quite comfortable demanding from our visual acuity tests, and it turns out at the moment the only convenient one out there that we know of is a letter chart.

DR. WEISS: Dr. Bradley, we get the idea you like the letter chart.

DR. BULLIMORE: He is so proud that he can read.

DR. WEISS: He likes that letter chart.

DR. BULLIMORE: He is so proud.

(Laughter.)

DR. WEISS: If there are no other comments on this, what I'd like to do then is move on to panel discussion on remaining issues, and I have three issues, and then we'll introduce if the agency has any additional issues or if any members of the panel want to introduce any additional issues.

One issue, which has been alluded to and discussed, but I would like to see if we can give as many opinions as possible, is duration of study before it's presented to the panel. Somewhere between two and three years has been mentioned. Perhaps any of those of you who would like to give your opinions can raise your hand and

just give me a number and tell me why.

Dr. Burns?

DR. BURNS: From what I see of the endothelial cell measurements and their likelihood of accuracy in this population, I think three years is a minimum.

DR. WEISS: So Dr. Burns feels three years.

Dr. Bullimore, had you -- three years. We have a sign. We're going to signs now. Okay. So we have Dr. Matoba at three, Dr. Grimmett at three. Dr. Bradley likes the number chart.

(Laughter.)

DR. WEISS: Dr. Huang, three. Dr. Mathers is three. Dr. Owsley is three. Dr. Swanson is three. So I think we have actually, even though we're not looking for a vote, essentially it's almost unanimous, if not unanimous, for three years.

DR. BANDEEN-ROCHE: Madam Chair?

DR. WEISS: Yes?

DR. BANDEEN-ROCHE: May I make a very brief comment?

DR. WEISS: Yes.

DR. BANDEEN-ROCHE: And that is that I believe it's important, based on Dr. Grimmett's comments, that at least one, preferably two, evaluations be scheduled between two and three years because he suggested that linearity was

not beginning to be achieved until then.

DR. WEISS: Okay. So one to two endothelial cell counts should be performed between the two- and three-year mark.

Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. I couldn't agree more with Dr. Bandeen-Roche that the data that is present in the peer-reviewed literature do not show a linear approach. We don't have enough data long enough. So that is correct. In an intermediate point.

DR. WEISS: Dr. Mathers?

DR. MATHERS: I would not end the data collection necessarily with three years because I think that ongoing data could be important.

DR. WEISS: That's an important question in terms of a postmarket study. It could be brought to panel at three years, at least from the recommendations from this panel today. After that, a postmarket study of what duration of time would you like to see, Dr. Mathers?

DR. MATHERS: Another two years.

DR. WEISS: Another two years.

Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. I would agree with Dr. Mathers' sentiments, but that decision would be made more accurately with the data in hand with the PMA at

three years obviously, but I would feel certainly comfortable with probably a postmarket study.

DR. MATHERS: Yes.

DR. WEISS: Dr. Bullimore?

DR. BULLIMORE: This is endothelium only?

DR. WEISS: It can be whatever you want.

DR. MATHERS: Cataract.

DR. WEISS: And you don't have to define it now. Basically, what the agency would like is your opinions.

DR. BULLIMORE: My opinions will be more well-informed once I have some data, but I have considerable concerns about the long-term safety of these intraocular devices. As the lens continues to grow, as it gets to cohabit with the phakic IOL for a long period of time, I don't think any of us can predict with any accuracy or precision what that's going to do to the crystalline lens on a long-term basis.

You know, these devices we can expect to be better than some of the first-generation phakic intraocular lenses, but they haven't been around long enough for us to tell, so I could foresee a substantial -- i.e., five-year -- postmarket study to track these patients and see, for example, how many people develop significant lens opacity, whatever that may be, how many people have to have a

cataract extraction and conventional IOL implantation, how many of those patients have complications from that procedure, and it can be nothing more than fairly straightforward head counting, but I think tracking these patients long-term, given what we know happened with, for example, extended wear contact lenses in the '80s and anterior chamber intraocular lenses, I think it would be prudent.

DR. WEISS: So the impression I get -- and if there's something you would like to add, then we'll add it -- is that the panel members would like to see postmarket studies from two years on up, maybe even to five years, but pending what the data shows.

DR. BULLIMORE: Once we have a PMA before us, we can make a more informed decision, but certainly, given the fact that this is an intraocular device that's cohabiting with a lens that's continuing to grow and function, I would --

DR. WEISS: You want to see a postmarket study.

DR. BULLIMORE: Well, I would anticipate the possibility of this requirement.

DR. WEISS: Dr. Mathers?

DR. MATHERS: We have not focused on pigment dispersion, but in the literature there are a number of papers that do. Not so much that they've had a lot of

glaucoma yet, but they often have pigment dispersion in the range of 30 percent, and therefore gonioscopy and pressure measurement.

DR. WEISS: Actually, that's an excellent point. I don't recall if that's in the document, gonioscopy, and then how often --

DR. MATHERS: It is.

DR. WEISS: And how often should postop.

DR. MATHERS: It's in there now and it hasn't been focused on, but it's in the literature, and I think it's an important issue.

DR. WEISS: So we haven't defined here, but there is concern in terms of follow-up as far as not only the cataract and the endothelium, but also gonioscopy and how frequently that would be done and what the postmarket would be would be defined in terms of when some of the data comes in.

Another question is what is an independent entity? Is the subject an independent entity or is the eye an independent entity?

For example, classically, for intraocular lenses, each patient has been an independent entity. Each subject has been an independent entity. So if the FDA statistically said that 300 data points were required, then each patient would be considered separately an entity

whether or not they had one or both eyes treated.

On the other hand, for LASIK, each eye has been considered an independent entity in the same patient, so that if 300 data points were required, then you might only need 150 patients.

So this is a very important point for sponsors to know whether they need 300 patients, and we're going to be getting to sample size as well, but if the sample size is determined to be necessary to be 300, should that be 300 patients or can it be 150 patients with both eyes treated?

Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Yes, I mean, statistically speaking, from a strict point of view, sites are the independent entities. Now, obviously, we're not going to base sample size on that, but methods are available to account for correlation of eyes within individuals, and in turn, of individuals within sites if necessary in computing power.

So one doesn't necessarily need to go to the extreme of saying, for instance, we're going to count people as entity. One can still account for the information provided by two eyes within an individual, yet accounting for the correlation in that information that two eyes shouldn't count as much as two separate people, and indeed that perhaps two people within a site shouldn't

count as much as two people in different sites.

I actually have a figure that I brought on this, but if you prefer to save it, we can.

DR. WEISS: No, sure.

DR. BANDEEN-ROCHE: I need the overhead. So can I just quickly set that up?

DR. BANDEEN-ROCHE: Sure. Maybe while you're setting that up, we can go on to a comment by Dr. Burns, and then to Dr. Matoba.

DR. BURNS: Yes, I just want to support that strongly because we're talking here a lot about biological reactions to a foreign body. So there will be a significant amount of correlation, I assume, between eyes, and so the studies should explain how they're going to handle it statistically in the design, and not in post-hoc analyses.

DR. WEISS: So I want to understand. Would you feel that an eye should be an independent entity or a subject?

DR. BURNS: I think Karen is going to explain the statistical way to handle it, but it's important that it be handled that way from the outset, that you're accounting for the correlation between eyes.

DR. WEISS: Now, we're going to go along with other comments, but we also need to look at this not only

statistically, but from a safety standpoint because this is a new device.

Dr. Matoba?

DR. MATOBA: Yes, in regard to the safety standpoint, since we've already decided that because of the issues of quality of life we're going to allow patients to have both their eyes done instead of limiting it to one eye over a three-year period of time, we might as well get data from both eyes, and so fewer people would have to be involved in the initial study.

DR. WEISS: Dr. Mathers?

DR. MATHERS: Yes, I strongly agree with that comment. I think we should have both eyes, but we should account for the correlation, and that allows us to get over this quality of life issue, which is going to be very, very important to the patient because only doing one eye is not going to work.

DR. WEISS: Well, we're not talking about only doing one eye. We're talking about whether you need 300 subjects who can both have both eyes done or 150 subjects who can still both have both eyes done.

DR. MATHERS: I think we shouldn't throw away the data on the second eye, but we should use it with an appropriate correlation.

DR. WEISS: So you basically want to count it

and not require another 150 patients.

DR. MATHERS: We're about to hear how we can account for the correlation.

DR. WEISS: Okay.

DR. MATHERS: In estimate.

DR. BANDEEN-ROCHE: Yes, and so certainly one can just state what is the expected design, including eyes within patients, patients within sites, et cetera, and then do power and all other statistical analyses accounting for that correlation. So what I had diagrammed here was thinking of people within sites, but it could equally well apply to eyes within people. There might be several levels.

So here, M is referring to the larger level. So let me just stick to people within sites because that's the way that I did it. So M is the number of sites and N is the number of individuals within sites.

So for instance, if it were people and eyes, it would be M people, and for two eyes, N would be two eyes per person, and so what I'm showing you here is the standard deviation of the mean -- say, a rate, say, a safety rate -- or I guess to simplify things, this was meant to be a continuous measure. So it would be something more like an acuity measure that's measured on a continuous scale.

So you can see that the standard deviation depends both on the overall number of units, either people times eyes or sites times people, and the symbol rho, which I'll point to here, that's the correlation between outcomes within a person -- so two eyes within a people -- or between visual acuities within a site, and then sigma is just the standard deviation of the measurement that's being taken in the population.

So one thing to point out is that if N equals 1, then this top term goes away, and you just get the usual standard deviation of the mean.

So what I'm showing you here is how the standard deviation varies for the -- I assumed the FDA sample size of 300, but what's varying here is the number of clusters, and so here's where this is really more relevant to sites and people within sites, because the FDA guidance for the number of sites says something like at least 20 per site and no more than a quarter being accounted for by any one site, and so if we had four sites, then that would just be meeting no more than a quarter by any one site. Then here, up at 300, you only have one patient per site, so that's the outer limit.

So the bottom line here, the straight line, is what you get if there's no correlation. That's just the standard deviation of the mean. If there's no correlation,